PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Glucose-lowering drugs and outcome from COVID-19 among patients with type 2 diabetes mellitus: a population-wide analysis in Hong Kong
AUTHORS	Luk, Andrea; Yip, Terry C.F.; Zhang, Xinge; Kong, Alice Pik Shan; Wong, Vincent Wai-Sun; Ma, Ronald; Wong, Grace

VERSION 1 – REVIEW

REVIEWER	Khunti, Kamlesh University of Leicester, Department of Health Sciences
REVIEW RETURNED	19-Aug-2021

GENERAL COMMENTS	This paper using a Hong-Kong population based database examined the association of glucose lowering therapies to outcomes from Covid-19 in people with type 2 diabetes. This paper is a resubmission and the authors have made a number of changes requested by the reviewers. The cohort consists of 1220 patients with diabetes who were admitted to the Public Health Facilities in Hong-Kong with the confirmed diagnosis of Covid-19. Multivariate cox regression was used to examine the association of pre-admission glucose lowering therapies with composite clinical outcomes. However, the total of number of people in the multivariate analysis was reduced to 737 patients. Overall the paper is well written. Overall the study found that on adjusted analysis metformin use was associative with a 49 % lower risk and DPP4 inhibitors a 54 % lower risk of composite outcomes of intensive care unit admission, requirement of invasive mechanical ventilation and/or in hospital deaths. Surprisingly use of sulphonylurea was associated with worse outcomes as well as the known worse association with Insulin. This cohort for this paper is relatively small compared to many papers that have been published in this area including those from England, US and France. Secondly there a number of limitations in terms of the data with most important omission being lack of BMI data. BMI has been shown to be independently associated with Covid-19 outcomes and BMI is also a major confounding factor when considering glucose lowering therapies. The study cohort is from the Hong-Kong hospital authority which provides care for approximatively 10 % of the local residents. It would be useful to have some information on how different this population is compared to the entire Hong-Kong population. The diagnosis was based on a number of criteria with one being a fasting glucose greater than 7 mmol/l although only 25 patients were identified based on a single fasting glucose. These patients may not have diabetes and the authors could consider conducting sensitivity analysis without these 25 patients. In Table 1 they

	report metabolic parameters and include BMI although the number of people with BMI was very small (9.3%) and this should be removed. It would also be good to have a column with missing numbers. Looking at Table 1 it also seems that all 737 patients in the analysis were on metformin but the baseline “drug use” column does not seem to match the numbers. For example 352 were on sulphonylurea and 343 were not but the percentages are reported as 91.4% and 50.5 % respectively. Similarly for all other columns. Other major areas for clarification are the composite outcomes whether they were mutually exclusive as that is not clarified. For example, the results on page 12 show that during admission 235 patients developed composite primary outcomes which included 187 patients transferred to ICU, 110 patients requiring mechanical ventilation and 90 patients who had died-these add up to 387 patients. The authors need to therefore clarify how they accounted for these outcomes. It would also be useful to present the absolute rates per 1000 person years for the glucose lowering drugs and no drugs as this would give an indication of whether the risk difference was clinically meaningful. The authors in the discussion state that the results could be confounding by indication, however, a number of very large studies have also concluded this and I wonder what the novelty is. Reviewer 3 had suggested potentially conducting a meta-analysis although the authors responded that due to competing resources they would not have the manpower to conduct this. I think this could be potential way of getting this into high impact journal. Other weakness is that they have not reported in their discussion the meta-analysis that have been published on glucose lowering agents and Covid-19 outcomes. They need to include these meta-analysis in the discussion and discuss how their results compare with those in the meta-analysis. For example for metformin there are 2 meta-analysis which include Lukito AA et al, (Diabetes & Metabolic Syndrome, 2020) and Kow CS et al (Journal Of Medical Virology, 2020). The meta-analysis for DPP4 inhibitors include Rakhmat et al, (Diabetes and Metabolic Syndrome 2021) and Hariyanto et al, (Diabetes and Metabolic Syndrome 2021). In the discussion the authors mention that their findings corroborate and extend the results of previous studies and suggest possible protective effect on metformin and DPP4 inhibitors. Although, metformin has certainly been shown to be associated with lower severe outcomes (see meta-analysis mentioned above), the data for DPP4 inhibitors are rather inconsistent. Furthermore this study cohort is small compared to other larger studies mentioned previously. The novel aspect of this study is that they have a number of inpatients biomarkers such as inflammatory markers, white cells counts which have not been reported well in previous studies. However, they did not adjust for some of these inpatient inflammatory markers which would be a novel analysis.

REVIEWER	Lukito , Antonia Anna Pelita Harapan University, Cardiovascular
REVIEW RETURNED	04-Sep-2021

GENERAL COMMENTS	Congratulations to the authors for this interesting manuscript, which may be applicable to predict outcomes in patients infected with COVID-19 based on background use of glucose-lowering drugs. This manuscript is easy to read, and interesting. The title and abstract cover the main aspects of the work.

	The methodology is clear and replicable. The statistical analysis is appropriate The content and conclusion are relevant.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Comment:
This paper using a Hong-Kong population based database examined the association of glucose lowering therapies to outcomes from Covid-19 in people with type 2 diabetes. This paper is a resubmission and the authors have made a number of changes requested by the reviewers. The cohort consists of 1220 patients with diabetes who were admitted to the Public Health Facilities in Hong-Kong with the confirmed diagnosis of Covid-19. Multivariate cox regression was used to examine the association of pre-admission glucose lowering therapies with composite clinical outcomes. However, the total of number of people in the multivariate analysis was reduced to 737 patients. Overall the paper is well written.
Overall the study found that on adjusted analysis metformin use was associative with a 49 % lower risk and DPP4 inhibitors a 54 % lower risk of composite outcomes of intensive care unit admission, requirement of invasive mechanical ventilation and/or in hospital deaths. Surprisingly use of sulphonylurea was associated with worse outcomes as well as the known worse association with Insulin.
This cohort for this paper is relatively small compared to many papers that have been published in this area including those from England, US and France. Secondly there a number of limitations in terms of the data with most important omission being lack of BMI data. BMI has been shown to be independently associated with Covid-19 outcomes and BMI is also a major confounding factor when considering glucose lowering therapies.
Response:
Thank you for the encouraging comments from the reviewer. Indeed we are also disappointed that we could not adjust for BMI given its strong relationships with outcome.

Comment:
The study cohort is from the Hong-Kong hospital authority which provides care for approximatively 10 % of the local residents. It would be useful to have some information on how different this population is compared to the entire Hong-Kong population.
Response:
Thank you for this comment. The Hong Kong Hospital Authority provides care for up to 80% of local residents. Given the high cost differential between the public and private healthcare sector with the private sector being significantly more expensive, people who utilise health services in the private sector are more likely to be at a more favourable socioeconomic position. This information is now included in the Methods section of the revised manuscript.

Comment:
The diagnosis was based on a number of criteria with one being a fasting glucose greater than 7 mmol/l although only 25 patients were identified based on a single fasting glucose. These patients may not have diabetes and the authors could consider conducting sensitivity analysis without these 25 patients.
Response:
Thank you for this comment. We conducted a sensitivity analysis excluding patients whose diabetes status was established based on a single fasting plasma glucose measurement. Exclusion of these patients did not significantly affect the results, as presented in Supplementary Table 6 of the revised manuscript.

Comment:
In Table 1 they report metabolic parameters and include BMI although the number of people with BMI was very small (9.3%) and this should be removed.
Response:
Thank you for this suggestion. The BMI data has been removed from Table 1.

Comment:
It would also be good to have a column with missing numbers.
Response:
Thank you for this suggestion. A column with the number (percentage) of patients with available data has been added to Table 1.

Comment:
Looking at Table 1 it also seems that all 737 patients in the analysis were on metformin but the baseline “drug use” column does not seem to match the numbers. For example 352 were on sulphonylurea and 343 were not but the percentages are reported as 91.4% and 50.5 % respectively. Similarly for all other columns.
Response:
Thank you for this observation. We defined user of a glucose-lowering drug based on pre-admission use of the drug, and non-user based on non-use before hospital admission and during hospital admission. Patients who were initiated glucose-lowering drug during hospital admission but was not using the drug before admission would not be counted as either user or non-user, and were excluded. In the highlighted example of sulphonylureas, there were 385 users and 679 non-users of sulphonylureas. The total number of users and non-users of sulphonlyureas (385 + 679 = 1,064) do not add up to the total number of patients with diabetes in this cohort (n=1,220) because 156 patients were initiated sulphonylureas during hospital admission but were not users at baseline, therefore excluded.
It follows that within this combined group of users and non-users of sulphonlyureas (n=1,064), the number of users (n=352) and non-users (n=343) of metformin will not add up to the total number of users (n=737) and non-users (n=254) of metformin in the metformin analysis.
The proportion of “91.4%” refers to the proportion of sulphonylurea users who were using metformin at baseline, as 352 / 385 = 91.4%. Similarly, the proportion of “50.5%” refers to the proportion of sulphonylurea non-users who were using metformin at baseline, as 343 / 679 = 50.5%.

Comment:
Other major areas for clarification are the composite outcomes whether they were mutually exclusive as that is not clarified. For example, the results on page 12 show that during admission 235 patients developed composite primary outcomes which included 187 patients transferred to ICU, 110 patients requiring mechanical ventilation and 90 patients who had died-these add up to 387 patients. The authors need to therefore clarify how they accounted for these outcomes.
Response:
Thank you for this suggestion. For the development of the composite endpoint, we followed the patients from the date of COVID-19 diagnosis until the date of ICU admission, use of mechanical ventilation, in-hospital death, or discharge from hospital, whichever came first. For the development of individual clinical endpoints including ICU admission, use of mechanical ventilation, and in-hospital death, patients were followed from the date of diagnosing COVID-19 until the date of the occurrence of that individual clinical endpoint or discharge from hospital, whichever came first. The sentence "For the composite endpoint, patients were followed from the date of diagnosing COVID-19 until the date of ICU admission, use of mechanical ventilation, in-hospital death, or discharge from hospital, whichever came first. For the individual clinical endpoints, patients were followed from the date of diagnosing COVID-19 until the date of the occurrence of that individual clinical endpoint or discharge

from hospital, whichever came first" is now added to the Method section of the revised manuscript.

Comment:
It would also be useful to present the absolute rates per 1000 person years for the glucose lowering drugs and no drugs as this would give an indication of whether the risk difference was clinically meaningful.
Response:
Thank you for this suggestion. We have provided the absolute incidence rate of clinical outcome in Supplementary Table 4.

Comment:
The authors in the discussion state that the results could be confounding by indication, however, a number of very large studies have also concluded this and I wonder what the novelty is. Reviewer 3 had suggested potentially conducting a meta-analysis although the authors responded that due to competing resources they would not have the manpower to conduct this. I think this could be potential way of getting this into high impact journal. Other weakness is that they have not reported in their discussion the meta-analysis that have been published on glucose lowering agents and Covid-19 outcomes. They need to include these meta-analysis in the discussion and discuss how their results compare with those in the meta-analysis. For example for metformin there are 2 meta-analysis which include Lukito AA et al, (Diabetes & Metabolic Syndrome, 2020) and Kow CS et al (Journal Of Medical Virology, 2020). The meta-analysis for DPP4 inhibitors include Rakhmat et al, (Diabetes and Metabolic Syndrome 2021) and Hariyanto et al, (Diabetes and Metabolic Syndrome 2021).
Response:
Thank you for the comment and suggestion. We have incorporated the results of several meta-analyses into our discussion in the revised manuscript (reference 32, 33, 39).

Comment:
In the discussion the authors mention that their findings corroborate and extend the results of previous studies and suggest possible protective effect on metformin and DPP4 inhibitors. Although, metformin has certainly been shown to be associated with lower severe outcomes (see meta-analysis mentioned above), the data for DPP4 inhibitors are rather inconsistent. Furthermore this study cohort is small compared to other larger studies mentioned previously.
Response:
Thank you for this comment. The small sample size is indeed a limitation of the analysis which is acknowledged in the limitation section.

Comment:
The novel aspect of this study is that they have a number of inpatients biomarkers such as inflammatory markers, white cells counts which have not been reported well in previous studies. However, they did not adjust for some of these inpatient inflammatory markers, which would be a novel analysis.
Response:
Thank you for this comment. We have previously considered adjusting for inflammatory markers. However, we have decided against this approach because the inflammatory markers are themselves indicators of COVID-19 severity rather than mediators of the association between glucose-lowering drugs and clinical outcome.

Reviewer: 2
Comments:
Congratulations to the authors for this interesting manuscript, which may be applicable to predict outcomes in patients infected with COVID-19 based on background use of glucose-lowering drugs.

This manuscript is easy to read, and interesting.
The title and abstract cover the main aspects of the work.
The methodology is clear and replicable.
The statistical analysis is appropriate
The content and conclusion are relevant.
Response:
We thank the reviewer for the encouraging and positive comments on our work.